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ORIGINAL ARTICLE

Retrospective audit of Active Surveillance practice in favourable risk Prostate Cancer in a local patient cohort

Christine Mizzi, Keith Pace, Luke Portelli, Gerald Busuttil

Background

The aim of this audit is to review the local monitoring of favourable risk prostate cancer (CaP) patients under active surveillance (AS), the primary endpoints being determining cancer-specific survival (CSS), rate of development of metastatic disease, mortality and percentage of patients who required definitive treatment.

Methods

Men diagnosed with CaP between January 2010 and December 2015 who were candidates for AS were included. Prostate specific antigen (PSA) values, imaging and histology results were recorded. The standard used is European Association of Urology 2021 guideline on AS and landmark papers published in the past decade.

Results

56.3% of patients had biochemical, radiological or histological progression. Overall survival is 85.4%. CSS is 97.9%. Mortality is 2.1%, whilst 4.2% of patients developed metastatic disease. From the audited population, 36.4% eventually required radical treatment. There is a statistically significant difference between the vital status groups' PSA level at diagnosis (p=0.002), PSA velocity (p=0.0001) and PSA density (p=0.029). The mean length of follow-up is 6.33years.

Conclusion

The high CSS rate is testimony to the success of local AS programs. The wide range of cancer stage, grade and PSA levels of patients chosen for AS should raise the question of whether our selection criteria for AS are stringent enough.

Dr Christine Mizzi, MD, MSc, FEBU
Department of Surgery,
Mater Dei Hospital
Msida, Malta

Mr Keith Pace, MD, MSc, FEBU
Department of Surgery,
Mater Dei Hospital
Msida, Malta

Mr Luke Portelli, MD, MRCS, MSc
Department of Surgery,
Mater Dei Hospital
Msida, Malta

Mr Gerald Busuttil, MRCS, FEBU, FRCS (Urol)
Department of Surgery,
Mater Dei Hospital
Msida, Malta

Active surveillance (AS) is a management option for men with localized, well-differentiated prostate cancer (CaP) considered to be at low risk of progression, in which invasive treatment is deferred till there is evidence of disease progression, or the patient expresses a desire for definitive treatment.[1] This avoids toxicity from overtreatment of clinically insignificant cancers without compromising long-term cancer-specific survival (CSS), by attempting to achieve the ideal timing for initiation of curative treatment. Through AS, patients are closely monitored by serum prostate specific antigen (PSA) levels, multiparametric magnetic resonance imaging (mpMRI) and prostate biopsies. When pre-defined thresholds are reached that signify curable but more serious disease, the patient should be offered definitive treatment.

OBJECTIVES

The aim of this audit is to review how favourable risk CaP patients under AS were monitored over recent years and to determine the proportion of men who had stable disease or eventually progressed to potentially life-threatening disease. The primary endpoints are to calculate CSS in patients on AS, rate of development of metastatic disease, mortality and to determine the percentage of patients who eventually switched to definitive treatment. The secondary outcomes of the audit are to record demographics and cancer characteristics of Maltese men diagnosed with favourable risk CaP such as age at diagnosis, histology and PSA kinetics and to develop correlations between this data and disease progression. Finally, we aim to determine whether the modalities used in follow-up, namely imaging, transrectal prostate biopsies and PSA serum levels are being performed locally in accordance to established guidelines and contemporary literature.

MATERIALS AND METHODS

This retrospective audit includes data on 96 Maltese patients diagnosed with favourable risk CaP enrolled onto AS within a 6 year period. Data protection clearance was obtained prior to data collection. All data was anonymised in a database. Data was collected by analysing all prostate biopsy histology reports showing adenocarcinoma of the prostate graded Gleason 6 (3+3), Gleason 7 (3+4) and Gleason 7 (4+3), issued by the histopathology department at Mater Dei Hospital between January 2010 and December 2015. All men diagnosed with favourable risk CaP who were candidates for AS during that time period were included in the study. Patient demographics, PSA values, imaging and histology results were manually retrieved from iSoft Clinical Manager. Censor date was taken to be either date of patient death or date of last follow-up appointment with the urologist or oncologist. Descriptive analyses were performed using Access Database. Statistical Package for the Social Sciences (SPSS) software was used for statistical analysis tests. The standard referred to is European Association of Urology (EAU) 2021 guideline on AS, along with landmark papers published in the past 10 years which were utilized in the development of the same guideline.

RESULTS

Baseline Demographics

The mean age at diagnosis with favourable risk CaP in the selected population was 69.4 years. The youngest patient was diagnosed at 49 years and the oldest at 86 years.

The mean PSA at diagnosis was 7.86 ng/ml. The PSA density was worked out as the PSA value divided by prostate volume, and the mean value was found to be 0.19 ng/ml^2 The mean PSA velocity was 0.9 ng/ml per year.

Only 11.5% of patients (11 individuals) had a pre-biopsy mpMRI performed. The tumour volume on diagnostic MRI was reported only in rare instances, but the mean tumour volume from the available reports was found to be 2ml. The prostate gland volume ranged widely from 20ml to 227ml, with the mean volume being 51.8ml. With regards to local staging on mpMRI, 20.8% of patients (20 men) had T2a disease, 1% (1 patient) T2b, 8.3% (8 patients) T2c and 2.1% (2 patients) T3a. Local staging was noted available for 67.7% of patients (65 cases).

The histological diagnosis in 85 patients was obtained through transrectal systematic biopsies. Four patients had fusion targeted biopsies. In the remaining 7 patients, adenocarcinoma was diagnosed incidentally from transurethral resection of the prostate (TURP) chippings. The majority of patients on AS (83 men, 86.5%), as expected, had Gleason 6 (3+3) tumours at diagnosis. Eight patients had Gleason 7 (3+4) disease at diagnosis, whilst the remaining 5 patients had higher grade Gleason 7 (4+3) tumours. A mean number of 10.7 cores were taken at biopsy. On average, there were 2.3 positive cores. The maximum cancer core length was not always specified in the histology report, however from the available data, the mean value was found to be 5.56mm.

Table 1 Biochemical, radiological and histological progression count

PSA progression	MRI progression	Histological progression	Count
Yes	Yes	Yes	4
Yes	Yes	No	11
Yes	No	Yes	5
Yes	No	No	23
No	Yes	Yes	3
No	Yes	No	7
No	No	Yes	1
No	No	No	42

Table 2 Vital status per PSA at diagnosis

Vital status	PSA at diagnosis		
	Minimum	Maximum	Mean
Alive - stable disease	1	23	7.25
Alive - progressive disease	1	25	9.13
Dead - cancer	8	8	8.00
Dead - other cause	5	9	7.11
Dead - unknown cause	15	19	17.33

Outcomes

In terms of biochemical follow-up, 44.8% of patients (43 men) had PSA progression. The mean level of PSA at progression was 13.3 ng/ml. The mean interval to PSA progression was 8.3 years.

With regards to radiological follow-up, our results show that 63.5% of the population (61 patients) had at least 1 follow-up MRI within the study period. This ranged from a minimum of 1 MRI to a maximum of 5 within 6 years, the mean being 2 MRIs. Out of all mpMRIs requested, 43 were as per AS protocol, whilst another 21 requests were prompted by PSA progression. One MRI was performed as follow-up to a previous MRI showing tumour progression. In 1 case, the indication for repeat MRI was not clear. Twenty-five patients were found to have tumour progression on MRI – 7 patients were re-staged at T2a, 3 at T2b, 10 T2c, 4 T3a and 1 patient was re-staged at T3b. The mean time to MRI progression was 8.9 years.

With regards to follow-up prostate biopsies, 30.2% of patients (29 individuals) underwent a repeat biopsy during the follow-up period. In 11 patients, biopsy was performed in view of PSA progression, in 8 patients in view of MRI progression, 4 as per proctocol, whilst no clear indication was found in 6 cases. When it comes to the type of biopsies performed, 19 were random biopsies, 8 were targeted and 2 were TURP specimens. The maximum number of follow-up biopsies in a single patient was 2. The mean number of repeat biopsies per patient from the subgroup that underwent follow-up biopsy was 1.04. Thirteen out of the 29 patients (44.8%) who had repeat biopsy were found to have histological progression – 8 patients progressed to Gleason 7 (3+4), 1 patient to Gleason 7 (4+3), 1 patient to Gleason 8 (4+4), 2 patients to Gleason 9 (4+5) and 1 patient progressed to Gleason 10. The mean time interval to histological progression was 3.98 years.

Table 1 shows that 56.3% of patients (54 individuals) had biochemical, radiological or histological progression. In the group with stable disease, the mean age at diagnosis was 55.9 years. The mean age at diagnosis of the group with disease progression was higher, at 62.6 years. Table 2 shows vital status counts per PSA level at diagnosis. Using the ANOVA (Analysis of Variance) test, allowing 95% confidence intervals, it was found that there is a statistically significant difference between the vital status groups' PSA level at diagnosis (p=0.002). Tables 3 and Table 4 correlate PSA kinetics and density with outcome. Using the ANOVA test, a statistically significant difference in PSA velocity was found between the vital status groups, allowing for confidence intervals of 95% (p=0.0001). There was also a statistically significant difference between groups in terms of PSA density (p=0.029, confidence intervals 95%). Table 5 gives further information on vital status per age at diagnosis. Table 6 show

Table 3 Outcome per PSA velocity

Vital status	Mean PSA velocity	Count
Alive - stable disease	0.27	67
Alive - progressive disease	2.99	15
Dead - cancer	5.11	2
Dead - other cause	-0.17	9
Dead - unknown cause	7.68	3

Table 4 Outcome per PSA density

Vital status	Count	Mean PSA density
Alive - stable disease	67	0.14
Alive - progressive disease	15	0.28
Dead - cancer	2	n/a
Dead - other cause	9	n/a
Dead - unknown cause	3	0.55

Table 5 Vital status per age at diagnosis

Vital status	Mean age
Alive - stable disease	68.8
Alive - progressive disease	69.3
Dead - cancer	78.2
Dead - other cause	69.6
Dead - unknown cause	76.8

Table 6 Disease progression per Gleason score at diagnosis

Diagnostic Gleason score	Stable disease no progression	Count
3+3	Yes	29
3+3	No	54
3+4	Yes	5
3+4	No	3
4+3	Yes	2
4+3	No	3

progression per Gleason score at diagnosis. Vital status of the various Gleason scores at diagnosis and of Gleason score at progression are found in Table 7 and Table 8.

A total of 35 patients (36.4 %) eventually required radical treatment, 32 in view of disease progression and 3 as per patient request. Definitive treatment consisted of external beam radiotherapy (EBRT) and androgen deprivation therapy (ADT) for 22 patients, EBRT alone in 2 patients, ADT alone in 7 patients and 4 men underwent radical prostatectomy (RP).

Final follow-up results show that 69.8% of patients (67 individuals) are alive with stable disease and 15.6% (15 patients) are alive with progressive

Table 7 Vital status per Gleason score at diagnosis

Gleason score at diagnosis	Vital status	Count
3+3	Alive - stable disease	62
3+3	Alive - progressive disease	14
3+3	Dead - other cause	6
3+3	Dead - unknown cause	1
3+4	Alive - stable disease	3
3+4	Dead - cancer	1
3+4	Dead - other cause	2
3+4	Dead - unknown cause	2
4+3	Alive - stable disease	2
4+3	Alive - progressive disease	1
4+3	Dead - cancer	1
4+3	Dead - other cause	1

Table 8 Vital status per Gleason score at progression

Gleason at progression	Vital status	Count
3+3	Alive - stable disease	62
3+3	Alive - progressive disease	10
3+3	Dead - cancer	1
3+3	Dead - other cause	7
3+3	Dead - unknown cause	3
3+4	Alive - stable disease	3
3+4	Alive - progressive disease	4
3+4	Dead - other cause	1
4+3	Alive - stable disease	1
4+4	Dead - other cause	1
9	Alive - progressive disease	1
9	Dead - cancer	1
10	Alive - stable disease	1

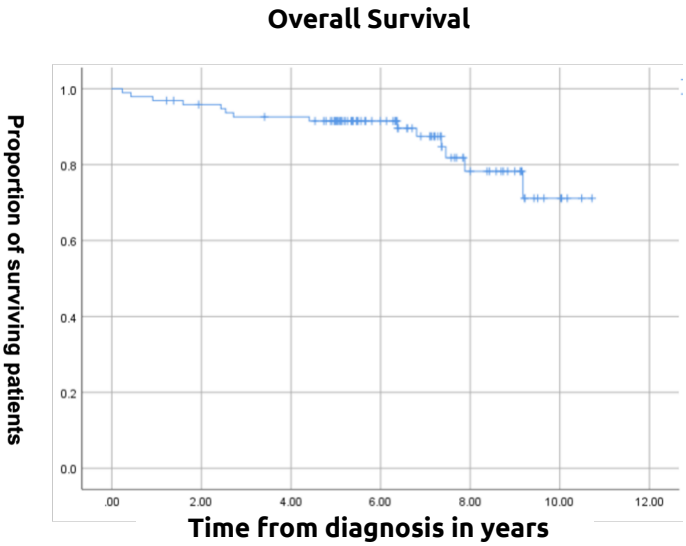

Figure 1 Kaplan-Meier curve showing overall survival

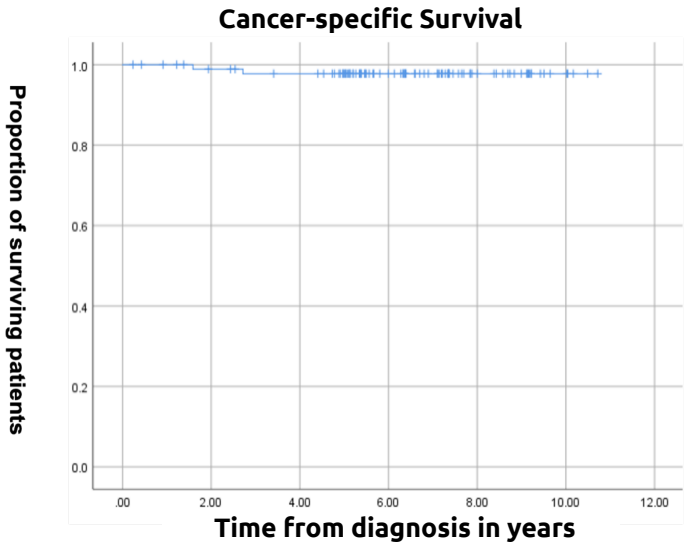

Figure 2 Kaplan-Meier curve showing cancer-specific survival

disease. Mortality from CaP cause is 2.1% (2 individuals), whereas 9.4% of patients (9 individuals) died from non-cancer related illness. Finally, 3.1% of patients (3 men) died from unknown cause. Overall survival (OS) was found to be 85.4%, as per Kaplan Meier curve in Figure 1. The Kaplan-Meier curve in Figure 2 shows CaP-specific survival which was worked out to be 97.9%. A total of 4 patients (4.2%) developed metastatic disease, of whom 2 are deceased of cancer cause and 2 are still alive. The mean time interval to the development of metastatic disease is 4.04 years. The mean length of follow-up for the entire population was 6.33 years.

DISCUSSION

CaP is one of the leading cancers worldwide and its incidence is expected to increase due to screening and early detection.[2] Life expectancy and health status play a crucial role in treatment decision. CaP is commoner in older men, the quoted mean age of diagnosis being 68 years.[3] This concurs with our findings, where the mean age at diagnosis was 69.4 years.

Uncertainties persists regarding optimal patient selection for AS and reliable progression criteria.[4] The eligibility criteria most often applied are International Society of Urological Pathology (ISUP) grade-1, tumour stage pT1c or pT2a, PSA<10ng/mL and PSA density<0.15ng/mL/cc. These criteria are supported by the DETECTIVE consensus, which also concluded that favourable ISUP-2 cancer (PSA<10 ng/mL, stage<pT2a, low number of positive cores) may be considered for AS but ISUP-3 disease should never be included.[5] There is significant variation between other studies regarding patient selection. In our cohort, selected men older than 70 years with intermediate-risk CaP (ISUP-2 and 3) were candidates for AS. This is justified by the fact that frail elderly patients with a poorer baseline health status gain less in terms of cancer-specific mortality with active treatment. Curative treatment is reserved for men with a life expectancy of at least 10 years.[6] From our results, at least 11 men had tumours more advanced than T2a at diagnosis and 17 patients had PSA higher than 10, yet were still considered for AS. Our local criteria for AS therefore seem to be more flexible than those traditionally recommended.

The surveillance protocol employed by Tosoian et al emphasized annual biopsy to avoid missing upgrading of cancers.[7] Locally, this is not standard practice since re-biopsy is usually prompted a rise in PSA or increase tumour burden on mpMRI. Thurtle et al report that MRI and PSA changes as sole triggers for re-biopsy detected 70% of progressions, whereas biopsy per protocol detected histological upgrading in only 7% of cases.[8] The DETECTIVE study concluded that repeat biopsies are indicated in case of progression on DRE, PSA or MRI; evidence for protocol-mandated biopsies is less robust.[5] Similarly, present guidelines are unclear on whether protocol mpMRI should be performed without clinical indication of progression. According to EAU guidelines, regular MRIs are increasingly used but their benefit and whether biopsy may be omitted based on MRI findings is controversial. The population audited here between 2010 and 2015 was managed mostly without the benefit of mpMRI, especially at diagnosis. This is a slightly different scenario to the current picture due to mpMRI being a more widely available resource nowadays. Nowadays,

most patients have a pre-biopsy MRI and regular MRIs thereafter whilst on AS.

Cancer grade is the most important factor for the prediction of CSS. A limitation of AS is that a significant proportion of patients with ISUP-1 cancer in fact harbour higher-grade disease. Definitive treatment is often recommended in the event of disease re-classification on biopsy.[7] From our results, 44.8% of patients who had repeat biopsy, had disease up-grading. In all cases, except for 3 patients, curative treatment was started. Literature states that 10% of patients on AS eventually request definitive treatment due to anxiety about their diagnosis.[9] Our results show a lower conversion rate (3.1%) from AS to active management strictly as per patient desire. The options of EBRT, RP or ADT were offered depending on co-morbidities and patient preference.

In the prospective series by Tosoian et al, 0.4% of patients on AS died from CaP or developed metastatic disease.[7] Our population, enrolled using less restrictive criteria and with less intensive monitoring, especially in terms of repeat biopsies, showed results more comparable to the study by Klotz et al[10] This reported that 3% of patients with low or intermediate risk CaP died or developed metastases at a median follow-up of 6 years. The local mortality rate of 2.1% and rate of metastatic disease of 4.2% are therefore consistent with expected outcome for low risk and select intermediate risk CaP. Mortality during AS highlights the attempt to balance overtreatment of cancer with the small, but real, risk of underestimating its fatality. Contemporary literature consistently shows excellent long-term OS and CSS of CaP patients on AS. Klotz et al report 10-year OS of 85%, comparable to our local OS of 85.4%.[10] They report CSS to be 98.1%, whilst our results show CSS of 97.9%. Tosoian et al report OS of 93% and CSS of 99.9%.[7] VanAs et al and Carter et al both report 10-year OS of 98% and CSS of 100%.[11,12]

A limitation of this audit is missing data which is crucial in determining adequacy of follow-up (e.g.if DRE was performed during visits, frequency at which PSA was taken). Radiological staging information is absent for 67% of patients. This is explained by the fact that up till recently, diagnosis of CaP relied on PSA levels and transrectal biopsies, without the benefit of mpMRI. Given the long natural history of CaP, follow-up is incomplete, despite the mean follow-up period of 6.33 years. The lack of pre-defined criteria in the recommendation for AS means that patients with higher grade disease who are normally not offered AS were included. This makes the cohort too heterogenous to derive solid conclusions on the safety of local AS programs.

CONCLUSION

AS is an ever-evolving strategy. There are no approved standards in follow-up protocols such as frequency of imaging with mpMRI, frequency of prostate biopsies, measurement of PSA kinetics and frequency of clinical examination with DRE, or when curative treatment should be initiated (i.e. re-classification criteria). Moreover, there is no consensus regarding which outcome measures are the best indicators of the disease progression and should therefore be prioritized. Individualized risk-based approaches to date replace protocol-based management of CaP patients on AS.

The value of this audit is that it provides the opportunity to compare our local practices in AS with those recommended by current guidelines and to recognize the areas that call for improvement. The high CSS rate is testimony to the success of local AS programs but could also be a reflection of the indolent behaviour of favourable risk CaP. On the other hand, scrutiny of cancer stage, grade and PSA levels of patients chosen for AS shows that the range is simply too wide. This should perhaps raise the question of whether our selection criteria for AS are stringent enough.

ABBREVIATIONS

ADT	androgen deprivation therapy
ANOVA	analysis of variance
AS	active surveillance
CaP	prostate cancer
CSS	cancer-specific survival
DRE	digital rectal examination
EAU	European Association of Urology
EBRT	external beam radiotherapy
ISUP	International Society of Urological Pathology
mpMRI	multi-parametric magnetic resonance imaging
OS	overall survival
PSA	prostate specific antigen
RP	radical prostatectomy
SPSS	Statistical Package for the Social Sciences
TURP	transurethral resection of the prostate

REFERENCES

1. Bruinsma SM, Roobol MJ, Carroll PR et al Semantics in active surveillance for men with localized prostate cancer — results of a modified Delphi consensus procedure. Nat Rev Urol 2017 May;14:(5)312–22.
2. Smith BD, Smith GL, Hurria A et al Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol Off J Am Soc Clin Oncol 2009 Jun 10;27:(17)2758–65.
3. Arnold M, Karim-Kos HE, Coebergh JW et al Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. Eur J Cancer Oxf Engl 1990 2015 Jun;51:(9)1164–87.
4. Thomsen FB, Brasso K, Klotz LH et al Active surveillance for clinically localized prostate cancer-a systematic review. J Surg Oncol 2014 Jun;109:(8)830–5.
5. Lam TBL, MacLennan S, Willemse P-PM et al EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study). Eur Urol 2019 Dec;76:(6)790–813.
6. Liu D, Lehmann HP, Frick KD et al Active Surveillance Versus Surgery for Low Risk Prostate Cancer: A Clinical Decision Analysis. J Urol 2012 Apr;187:(4)1241–6.
7. Tosoian JJ, Mamawala M, Epstein JI et al Intermediate and Longer-Term Outcomes From a Prospective Active-Surveillance Program for Favorable-Risk Prostate Cancer. J Clin Oncol Off J Am Soc Clin Oncol 2015 Oct 20;33:(30)3379–85.
8. Thurtle D, Barrett T, Thankappan-Nair V et al Progression and treatment rates using an active surveillance protocol incorporating image-guided baseline biopsies and multiparametric magnetic resonance imaging monitoring for men with favourable-risk prostate cancer. BJU Int 2018 Jul;122:(1)59–65.
9. Klotz L, Zhang L, Lam A et al Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol Off J Am Soc Clin Oncol 2010 Jan 1;28:(1)126–31.
10. Klotz L, Vesprini D, Sethukavalan P et al Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol Off J Am Soc Clin Oncol 2015 Jan 20;33:(3)272–7.
11. van As NJ, Norman AR, Thomas K et al Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. Eur Urol 2008 Dec;54:(6)1297–305.
12. Carter HB, Kettermann A, Warlick C et al Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. J Urol 2007 Dec;178:(6)2359–64; discussion 2364-2365.